REMARKS

The Office Action of February 24, 2004 has been received and its contents carefully considered.

Claims 14 to 29 are all the claims pending in the application, prior to the present amendment.

The Examiner, at page 2 of the Office Action, in a section entitled "Response To Applicants Comments About the Restriction", repeats his request for applicants to cancel all non-elected subject matter.

In response, applicants have amended the claims to direct them to verapamil as the second drug and to cancel claims 20, 28 and 29. The present claims do not preclude the use of another drug in addition to verapamil as a second drug.

Claims 14, 15 and 20 have been rejected under 35 U.S.C. § 102(b) as anticipated by Pritchard et al.

Applicants submit that Pritchard et al do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

The present invention, as set forth in claim 14, is directed to a method of administering a drug with binding affinity for plasma protein, wherein, in the administration of a first drug with binding affinity for plasma protein, a second drug, which is verapamil, with binding affinity for the same plasma protein for which the first drug has binding affinity, is administered simultaneously with the first drug or before or after the administration of the first drug to thereby regulate the binding of the first drug to the plasma protein.

Applicants have previously argued that Pritchard et al do not disclose or suggest that verapamil can be used as a second drug to regulate the binding of bepridil, since Pritchard et al disclose that the amount of verapamil in Pritchard et al is necessary to affect the binding is greater than the amounts that are clinically employed.

The Examiner acknowledges that applicants have argued that Pritchard et al do not teach the present invention because the amount of verapamil in Pritchard et al necessary to effect the binding is greater than the amounts that are clinically employed.

In response to this argument, the Examiner asserts that independent claim 14 reads on both *in vivo* and *in vitro* methods, whereas claims 16 to 19 and 21 to 29 are directed to *in vivo* methods or compositions.

The Examiner states that since claims 14, 15 and 20 are not limited to *in vivo* administration, there are no requirements in these claims that the amounts administered be pharmaceutically acceptable or an effective amount. The Examiner states that the method of claims 14, 15 and 20 simply requires the administration of a first drug and a single/plural second drug, where both drugs having binding affinity for the same plasma protein. The Examiner, therefore, concludes that applicants' argument regarding the amount of verapamil administered is not persuasive.

In response, applicants have amended claim 14 by adding to the term "*in vivo*" before the word "administration" in claim 14.

In view of the above, applicants submit that Pritchard et al do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

Claims 14 to 17, 20, 21, 23, 25, 28 and 29 have been rejected under 35 U.S.C. § 102(b) as anticipated by Somogyi et al for reasons of record and for additional reasons set forth at page 4 of the Office Action.

Applicants submit that Somogyi et al do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

At page 4 of the Office Action, the Examiner acknowledges that applicants have stated that the Examiner is of the opinion that both an intravenous dose and oral dose of verapamil are administered simultaneously in Somogyi et al.

The Examiner specifically refers to page 52 to columns 1 and 2, the bridging paragraph, as disclosing that verapamil was administered by intravenous and oral route simultaneously using stable labeled techniques and that the intravenous (unlabeled) dose was given at a constant infusion of 10 mg verapamil dissolved in 10 ml physiologically saline over five minutes and the oral dose of 40 mg HCl consisted of d_3-verapamil given in solution form 30 minutes after the end of the intravenous infusion. The Examiner also points out that Somogyi et al disclose that the controlled subjects received the same intravenous doses, but 80 mg d_3-verapamil orally.

Applicants do not dispute that Somogyi et al disclose the simultaneous administration of verapamil by both intravenous and oral route. Applicants do not see how this point is relevant to the Examiner's rejection.

The point that applicants were making with respect to the disclosure of Somogyi et al is that Somogyi et al nowhere disclose the administering of a second drug that regulates the binding of the first drug to the plasma protein.

The Examiner acknowledges that applicants have argued that Somogyi et al do not discuss binding to plasma proteins, and only mentions the binding to plasma protein in item 4 of the abstract and the discussion on page 55.

In response to this argument, the Examiner directs applicants' attention to page 52 of Somogyi et al and the section entitled "Plasma protein binding and erythrocyte distribution".

The Examiner is correct that Somogyi et al, at page 52, contain a section that discusses plasma protein binding, but as discussed below, Somogyi et al nowhere disclose or suggest the administering of a second drug that regulates the binding of the first drug to the plasma protein.

Applicants have reviewed the entire Somogyi et al article and set forth the following comments on the disclosures in Somogyi et al that discuss plasma protein binding.

The discussion at page 52 that the Examiner has referred to, which continues on to page 53, merely discusses how the protein binding of verapamil was determined, and does not set forth any of the results of the determination. Thus, the discussion at pages 52 and 53 does not indicate that a second drug regulated the plasma protein binding of the first drug.

Moreover, the procedure set forth at pages 52 and 53 would not be able to determine whether a second drug regulated the plasma protein binding of the first drug because the procedure does not measure the plasma protein binding with a first drug and compare it to the plasma protein binding obtained with a first and second drug. The procedure merely measures the plasma protein binding at different concentrations of a single drug.

The places where Somogyi et al do disclose the results of that determination are as follows:

(i) In the abstract, in item 4, Somogyi et al state that "Plasma protein binding remained unchanged." As discussed in subsections (ii), (iii) and (iv) below, applicants submit that this indicates that the plasma protein binding was unchanged between healthy patients and liver cirrhotic patients.

(ii) At page 54, right hand column, last word, to page 55, left hand column, Somogyi et al contain the following discussion:

> In the liver cirrhotic patients, the free fraction of verapamil in plasma was on average 8.0 (range 7.3 to 8.9)% and was independent of the total verapamil concentration (P>0.05). This free fraction was not different to those reported by us (range 7.8 to 11.3%) previously (Schomerus *et al.*, 1976).

This discussion indicates that the plasma protein binding was unchanged between healthy patients and liver cirrhotic patients, and does not contain any information concerning regulation of the plasma protein binding by use of a second drug. To the extent it contains any information concerning the regulation of plasma protein binding by use of a second drug, it shows that there was no regulation.

Thus, this section of Somogyi et al indicates that plasma protein binding was unchanged between healthy patients and liver cirrhotic patients, and does not contain any information concerning regulation of the plasma protein binding by use of a second drug.

(iii) Somogyi et al, at page 55, left hand column, first complete paragraph, contains the following statement:

> The increased volume of distribution and unaltered plasma protein binding of verapamil resulted in an approximately 25% decrease, from 0.73 to 0.5% in the free fraction bound to tissues (see **Methods**).

This discussion in Somogyi et al confirms that Somogyi et al teach that plasma protein binding was unchanged, that is, there was an "unaltered plasma protein binding".

Again, this discussion means that the plasma protein binding was unchanged between healthy patients and liver cirrhotic patients.

(iv) Somogyi et al, at page 58, left hand column, under the heading "Discussion" state as follows:

> Since protein binding remained unchanged an approximately 25% decrease in the free fraction bound to tissue is calculated which together with the 28% increase in total body water (Schober *et al.*, 1979) is proposed to explain the increased volume of distribution.

Again, applicants submit that this disclosure in Somogyi et al indicates that there was no change in the plasma protein binding between healthy patients and liver cirrhotic patients, and does not contain any information concerning regulation of the plasma protein binding by a second drug. (Applicants note that in the Amendment Under 37 C.F.R. § 1.111 filed on November 24, 2004, at page 12, as the result of a typographical error, they had indicated that the "Discussion" appeared at page 55 of Somogyi et al).

In view of the above, applicants submit that Somogyi et al do not defeat the patentability of the present claims and, accordingly, request withdrawal of this rejection.

Claims 14 and 16 to 29 have been rejected under 35 U.S.C. § 103(a) as obvious over Somogyi et al in view of Li et al.

Applicants submit that these references do not disclose or render obvious the presently claimed invention and, accordingly, request withdrawal of this rejection.

Applicants have discussed Somogyi et al in detail above, and rely on that discussion.

Thus, as discussed above, Somogyi et al do not disclose or suggest the administering of a second drug that regulates the binding of the first drug to the plasma protein.

The Examiner, in a previous Office Action, had relied on the Li et al patent for a teaching of water-soluble polymer conjugate of "other therapeutic drugs" which include verapamil, and for a teaching of water-soluble pro-drugs. The Examiner stated that the complexes in Li et al may be radiolabeled with various metals or conjugated to various chelators, and that the complexes may be imaged using single photo emission computer topography or positron emission tomograpy. The Examiner stated that Li et al disclose that verapamil can be used in combination with another drug that may be radiolabeled.

The Examiner asserted that it would have been obvious to modify the invention of Somogyi et al et al by using the teachings of Li et al, and generate a kit comprising first and second drugs and attach various radiolabels and/or a chelators, because Li et al disclose a composition wherein verapamil may be added to generate a water soluble polymer conjugate.

Although the Examiner has stated that Li et al disclose that verapamil can be used in combination with another drug that may be radiolabeled, applicants have not found any such disclosure in Li et al. Li et al merely disclose that verapamil can be used to make a water soluble polymer conjugate, and that water soluble metal chelator conjugates of Li et al can contain a radionuclide in certain embodiments. Li et al disclose that the water soluble conjugates can be

administered in conjunction with other drugs, but do not disclose that these other drugs may be radiolabeled.

Further, Li et al do not supply the deficiencies of Somogyi et al that have been discussed above. Thus, Li et al do not disclose or suggest the administering of a second drug that regulates the binding of the binding of the first drug to plasma protein.

Since there is no disclosure or suggestion in Samogyi et al or Li et al with regard to the regulation of the plasma protein binding of a first drug by administering a second drug, applicants submit that one of ordinary skill in the art could not arrive at the present invention from the combined teachings of Samoygi et al and Li et al.

In view of the above, applicants submit that the cited references do not defeat the patentability of the presently claimed invention and, accordingly, request withdrawal of this rejection.

The Examiner acknowledges that applicant is correct that the present application was not filed under 37 C.F.R. § 1.60. The Examiner asks applicants to insert the continuing data in the first line of the specification. In particular, the Examiner requests applicant to insert the phrase "This application is a 371 of PCT/JP00/04039 filed 6/21/00".

The Examiner, however, has not responded to applicants' position that the MPEP at §1893.03(c), page 1800-156 of Revision 1, February 2003, of the 8th Edition, specifically indicates that the National Stage Entry of PCT application does not have to contain as a first sentence a reference to the PCT application. Accordingly, applicants submit that they are not required to amend the specification in the manner suggested by the Examiner.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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